CALCILYTIC COMPOUNDS

FIELD OF INVENTION

The present invention relates to novel calcilytic compounds, pharmaceutical compositions containing these compounds and their use as calcium receptor antagonists.

In mammals, extracellular Ca^{2+} is under rigid homeostatic control and regulates various processes such as blood clotting, nerve and muscle excitability, and proper bone formation. Extracellular Ca^{2+} inhibits the secretion of parathyroid hormone ("PTH") from parathyroid cells, inhibits bone resorption by osteoclasts, and stimulates secretion of calcitonin from C-cells. Calcium receptor proteins enable certain specialized cells to respond to changes in extracellular Ca^{2+} concentration.

PTH is the principal endocrine factor regulating Ca^{2+} homeostasis in the blood and extracellular fluids. PTH, by acting on bone and kidney cells, increases the level of Ca^{2+} in the blood. This increase in extracellular Ca^{2+} then acts as a negative feedback signal, depressing PTH secretion. The reciprocal relationship between extracellular Ca^{2+} and PTH secretion forms an important mechanism maintaining bodily Ca^{2+} homeostasis.

Extracellular Ca^{2+} acts directly on parathyroid cells to regulate PTH secretion. The existence of a parathyroid cell surface protein which detects changes in extracellular Ca^{2+} has been confirmed. See Brown et al., Nature 366:574, 1993. In parathyroid cells, this protein, the calcium receptor, acts as a receptor for extracellular Ca^{2+}, detects changes in the ion concentration of extracellular Ca^{2+}, and initiates a functional cellular response, PTH secretion.

Extracellular Ca^{2+} influences various cell functions, reviewed in Nemeth et al., Cell Calcium 11:319, 1990. For example, extracellular Ca^{2+} plays a role in parafollicular (C-cells) and parathyroid cells. See Nemeth, Cell Calcium 11:323, 1990. The role of extracellular Ca^{2+} on bone osteoclasts has also been studied. See Zaidi, Bioscience Reports 10:493, 1990.

Various compounds are known to mimic the effects of extra-cellular Ca^{2+} on a calcium receptor molecule. Calcilytics are compounds able to inhibit calcium

receptor activity, thereby causing a decrease in one or more calcium receptor activities evoked by extracellular Ca^{2+}. Calcilytics are useful as lead molecules in the discovery, development, design, modification and/or construction of useful calcium modulators, which are active at Ca^{2+} receptors. Such calcilytics are useful in the treatment of various disease states characterized by abnormal levels of one or more components, e.g., polypeptides such as hormones, enzymes or growth factors, the expression and/or secretion of which is regulated or affected by activity at one or more Ca^{2+} receptors. Target diseases or disorders for calcilytic compounds include diseases involving abnormal bone and mineral homeostasis.

Abnormal calcium homeostasis is characterized by one or more of the following activities: an abnormal increase or decrease in serum calcium; an abnormal increase or decrease in urinary excretion of calcium; an abnormal increase or decrease in bone calcium levels (for example, as assessed by bone mineral density measurements); an abnormal absorption of dietary calcium; an abnormal increase or decrease in the production and/or release of messengers which affect serum calcium levels such as PTH and calcitonin; and an abnormal change in the response elicited by messengers which affect serum calcium levels.

Thus, calcium receptor antagonists offer a unique approach towards the pharmacotherapy of diseases associated with abnormal bone or mineral homeostasis, such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and osteoporosis.

SUMMARY OF THE INVENTION

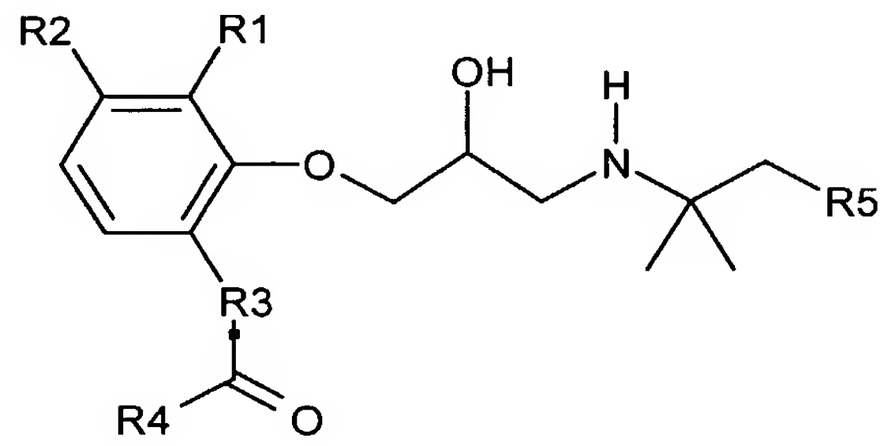
The present invention comprises novel calcium receptor antagonists represented by Formula (I) hereinbelow and their use as calcium receptor antagonists in the treatment of a variety of diseases associated with abnormal bone or mineral homeostasis, including but not limited to hypoparathyroidism, osteosarcoma, periodontal disease, fracture healing, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia associated with malignancy and fracture healing, and osteoporosis.

The present invention further provides a method for antagonizing calcium receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I), indicated hereinbelow.

The present invention further provides a method for increasing serum parathyroid levels in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I), indicated herein below.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are selected from Formula (I) herein below:



I

wherein:

R1 is selected from the group consisting of H, CN, and halogen;

R2 is selected from the group consisting of H, halogen, CN, NO_2, and SO_2R4

R3 is selected from the group consisting of C_{0-6} alkyl, and C_{0-6} alkenyl, optionally substituted;

R4 is selected from the group consisting of OH, OC_{1-7} alkyl, optionally substituted; NH_2, and NHR4

R5 is selected from the group consisting of aryl, fused aryl, dihydro, tetrahydro fused aryl, and heteroaryl, unsubstituted or substituted, with any substituent selected from the group consisting of OH, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, OCF_3, CN and NO_2.

As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined by single carbon-carbon bonds and having 1-20 carbon atoms joined together. The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or unsaturated. Preferably, substituents on optionally substituted alkyl are selected from the group consisting of aryl, CO_2R, CO_2NHR, OH, OR, CO, NH_2, halo, CF_3, OCF_3 and NO_2, wherein R represents H, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, heterocycloalkyl, or aryl. Additional substituents are selected from F, Cl, Br, I, N, S and O. Preferably, no more than three substituents are present. More preferably, the alkyl has 1-12 carbon atoms and is unsubstituted. Preferably, the alkyl group is linear.

As used herein "cycloalkyl" refers to optionally substituted 3-7 membered carbocyclic rings wherein any substituents are selected from the group consisting of, F, Cl, Br, I, $N(R_4)_2$, SR_4 and OR_4, unless otherwise indicated.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems. Aryl includes carbocyclic aryl, and biaryl groups, all of which may be optionally substituted. Preferred aryl include phenyl and naphthyl. More preferred aryl include phenyl. Preferred substituents are selected from the group consisting of halogen, C_{1-4} alkyl, OCF_3, CF_3, OMe, CN, OSO_2 R and NO_2, wherein R represents C_{1-4} alkyl or C_{3-6} cycloalkyl.
As used herein, "heteroaryl" refers to an aryl ring containing 1,2 or 3 heteroatoms such as N, S, or O.

As used herein, "alkenyl" refers to an optionally substituted hydrocarbon group containing at least one carbon-carbon double bond and containing up to 5 carbon atoms joined together. The alkenyl hydrocarbon chain may be straight, branched or cyclic. Any substituents are selected from the group consisting of halogen, C_{1-4} alkyl, OCF_3, CF_3, OMe, CN, OSO_2 R and NO_2, wherein R represents C_{1-4} alkyl or C_{3-6} cycloalkyl.

As used herein, "alkynyl" refers to an optionally substituted hydrocarbon group containing at least one carbon-carbon triple bond between the carbon atoms and containing up to 5 carbon atoms joined together. The alkynyl hydrocarbon

group may be straight-chained, branched or cyclic. Any substituents are selected from the group consisting of halogen, C_{1-4} alkyl, OCF_3, CF_3, OMe, CN, OSO_2 R and NO_2, wherein R represents
C_{1-4} alkyl or C_{3-6} cycloalkyl.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

Preferred compounds of the present inventions include:
3-{3,4-Difluoro-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid;
3-{3,4-Difluoro-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid ethyl ester;
3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-propionic acid;
3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-propionic acid ethyl ester;
3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-pentanoic acid;
4-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-butyric acid; and
4-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-butyric acid ethyl ester.

Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered.

Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate. A preferred salt is a hydrochloride. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic

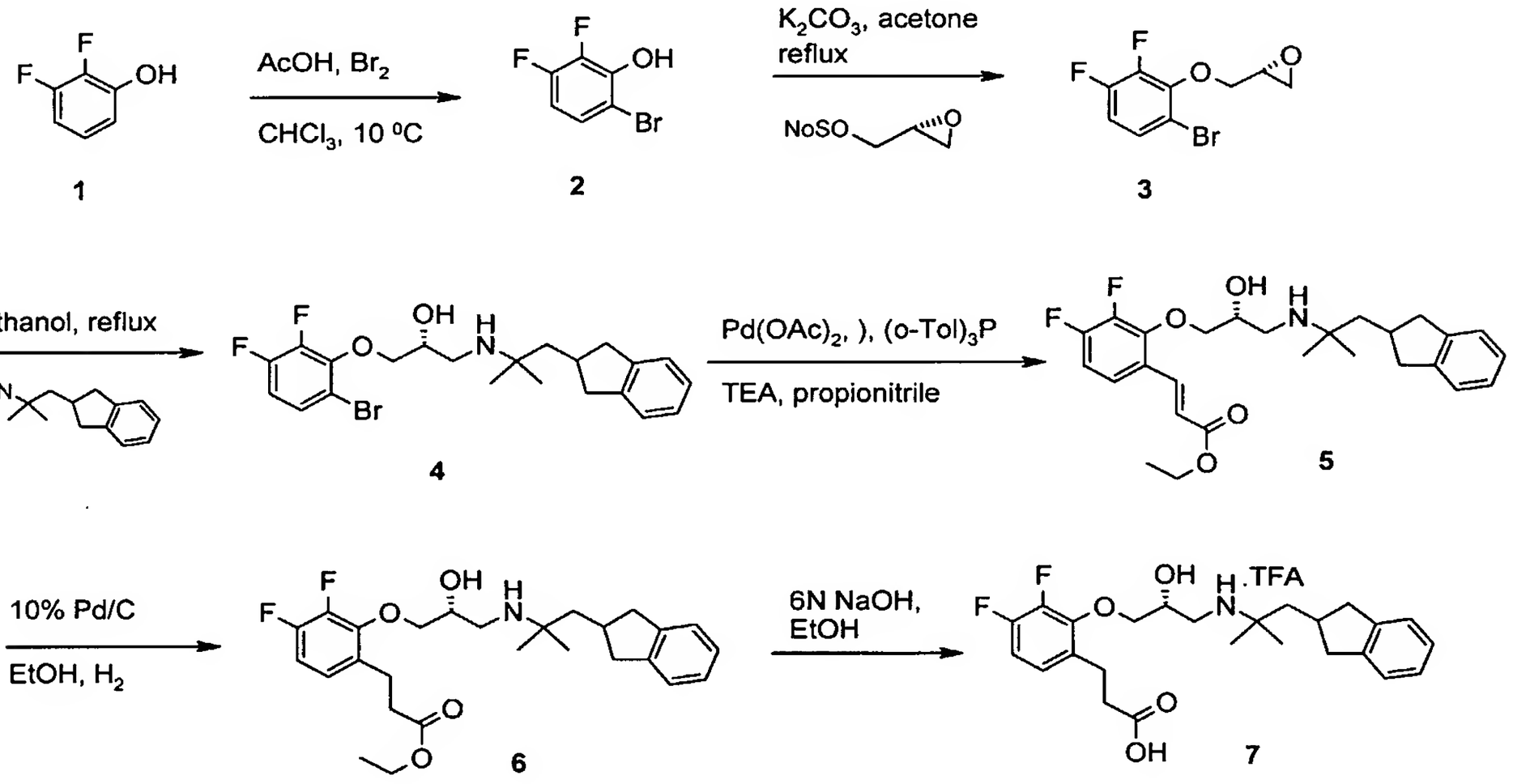
acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present.

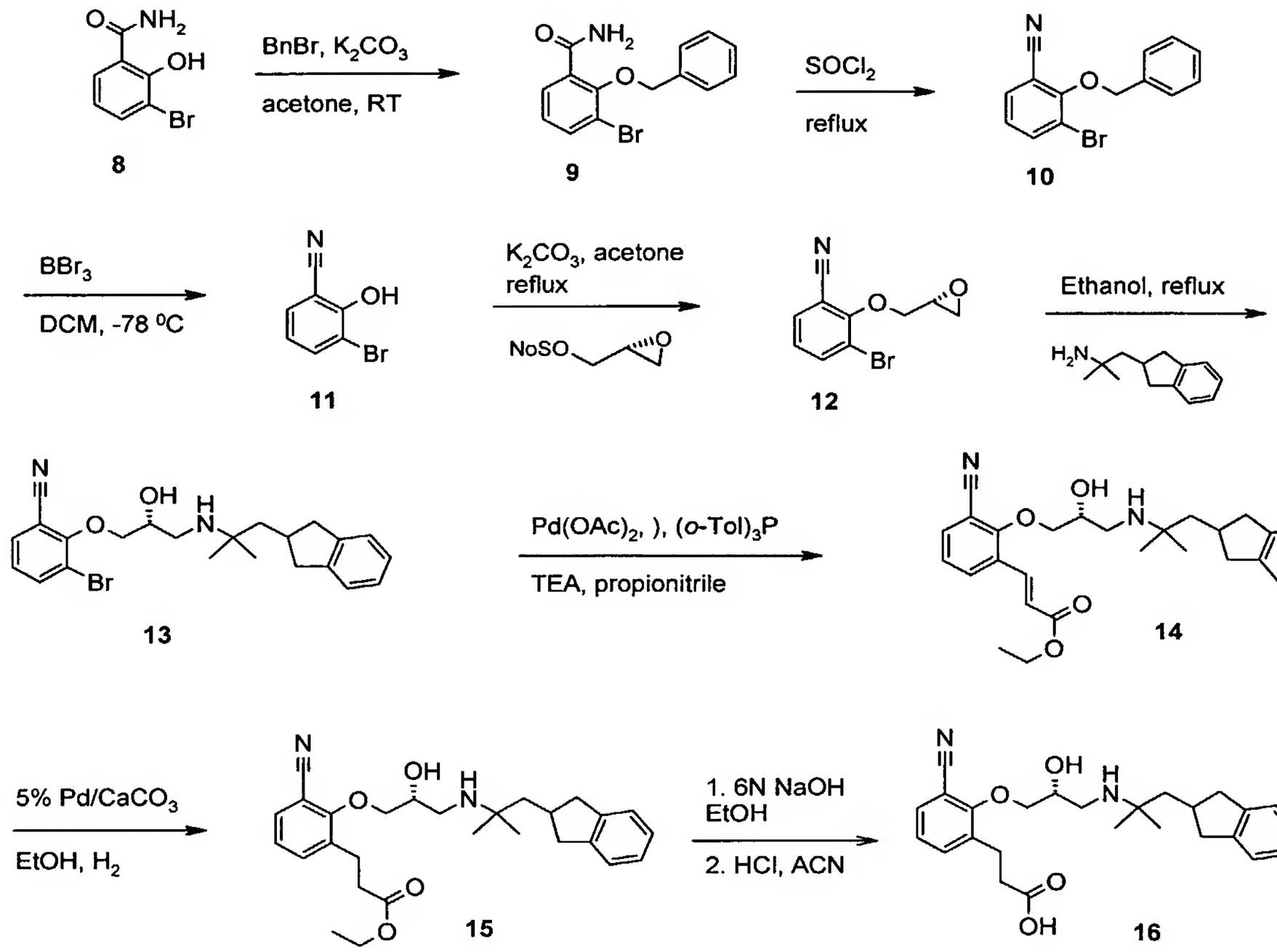
The present invention provides compounds of Formula (I) above, which can be prepared using standard techniques. An overall strategy for preparing preferred compounds described herein can be carried out as described in this section. The examples, which follow, illustrate the synthesis of specific compounds. Using the protocols described herein as a model, one of ordinary skill in the art can readily produce other compounds of the present invention.

All reagents and solvents were obtained from commercial vendors. Starting materials were synthesized using standard techniques and procedures.

Scheme 1



Scheme 2



General Preparation:

The synthesis of the compound of the general formula (I) may be prepared as outlined below in Schemes 1 and 2. Treatment of an appropriately substituted bromo-phenol **2** or **11,** which is obtained by methods common to the art, with a base such as potassium carbonate in the presence of a nosyl-protected glycidyl oxirane provides the epoxide intermediate **3** or **12**. Treatment of such an epoxide with a primary amine such as 2-indan-2-yl-1,1-dimethyl-ethylamine in a solvent such as ethanol or toluene at elevated temperature provides the amino alcohol **4** or **13**. Heck coupling of this aryl bromide with an olefin such as ethyl acrylate provides the α,β-unsaturated ester **5** or **14,** which can be saturated under conditions which are common to the art such as hydrogen in the presence of a catalyst such as palladium on carbon or calcium carbonate to provide the ester **6** or **15**.

Saponification of such an ester by treatment with a base such as sodium hydroxide in ethanol and water provides the corresponding carboxylic acid **7** or **16**.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The calcilytic compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, topical (transdermal), or transmucosal administration. For systemic administration, oral administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and subcutaneous. For injection, the compounds of the invention are formulated in liquid solutions, preferably, in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized forms can also be produced.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays, rectal suppositories, or vaginal suppositories.

For topical administration, the compounds of the invention can be formulated into ointments, salves, gels, or creams, as is generally known in the art.

The amounts of various calcilytic compounds to be administered can be determined by standard procedures taking into account factors such as the compound IC_{50}, EC_{50}, the biological half-life of the compound, the age, size and weight of the

patient, and the disease or disorder associated with the patient. The importance of these and other factors to be considered are known to those of ordinary skill in the art.

Amounts administered also depend on the routes of administration and the degree of oral bioavailability. For example, for compounds with low oral bioavailability, relatively higher doses will have to be administered.

Preferably the composition is in unit dosage form. For oral application, for example, a tablet, or capsule may be administered, for nasal application, a metered aerosol dose may be administered, for transdermal application, a topical formulation or patch may be administered and for transmucosal delivery, a buccal patch may be administered. In each case, dosing is such that the patient may administer a single dose.

Each dosage unit for oral administration contains suitably from 0.01 to 500 mg/Kg, and preferably from 0.1 to 50 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, calculated as the free base. The daily dosage for parenteral, nasal, oral inhalation, transmucosal or transdermal routes contains suitably from 0.01 mg to 100 mg/Kg, of a compound of Formula (I). A topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered, for example, from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

Diseases and disorders which might be treated or prevented, based upon the affected cells, include bone and mineral-related diseases or disorders; hypoparathyroidism; those of the central nervous system such as seizures, stroke, head trauma, spinal cord injury, hypoxia-induced nerve cell damage, such as occurs in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, and

Tourette's syndrome; diseases involving excess water reabsorption by the kidney, such as syndrome of inappropriate ADH secretion (SIADH), cirrhosis, congestive heart failure, and nephrosis; hypertension; preventing and/or decreasing renal toxicity from cationic antibiotics (e.g., aminoglycoside antibiotics); gut motility disorders such as diarrhea and spastic colon; GI ulcer diseases; GI diseases with excessive calcium absorption such as sarcoidosis; autoimmune diseases and organ transplant rejection; squamous cell carcinoma; and pancreatitis.

In a preferred embodiment of the present invention, the present compounds are used to increase serum parathyroid hormone ("PTH") levels. Increasing serum PTH levels can be helpful in treating diseases such as hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease, humoral hypercalcemia malignancy and osteoporosis.

In a preferred embodiment of the present invention, the present compounds are co-administered with an anti-resorptive agent. Such agents include, but are not limited estrogen, 1, 25 $(OH)_2$ vitamin D3, calcitonin, selective estrogen receptor modulators, vitronectin receptor antagonists, V-H+-ATPase inhibitors, src SH2 antagonists, bisphosphonates and cathepsin K inhibitors.

Another aspect of the present invention describes a method of treating a patient comprising administering to the patient an amount of a present compound sufficient to increase the serum PTH level. Preferably, the method is carried out by administering an amount of the compound effective to cause an increase in duration and/or quantity of serum PTH level sufficient to have a therapeutic effect.

In various embodiments, the compound administered to a patient causes an increase in serum PTH having a duration of up to one hour, about one to about twenty-four hours, about one to about twelve hours, about one to about six hours, about one to about five hours, about one to about four hours, about two to about five hours, about two to about four hours, or about three to about six hours.

In an alternative embodiment of the present invention, the compound administered to a patient causes an increase in serum PTH having a duration of more than about twenty four hours provided that it is co-administered with an anti resorptive agent.

In additional different embodiments, the compound administered to a patient causes an increase in serum PTH of up to two fold, two to five fold, five to ten fold, and at least 10 fold, greater than peak serum PTH in the patient. The peak serum level is measured with respect to a patient not undergoing treatment.

Composition of Formula (I) and their pharmaceutically acceptable salts, which are active when given orally, can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavoring or coloring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils, and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of a compound or salt in a sterile aqueous or non-aqueous carrier optionally containing parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogs.

Typical dermal and transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer a single dose.

No unacceptable toxological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

(I) Calcium Receptor Inhibitor Assay

Calcilytic activity was measured by determining the IC_{50} of the test compound for blocking increases of intracellular Ca^{2+} elicited by extracellular Ca^{2+} in HEK 293 4.0-7 cells stably expressing the human calcium receptor. HEK 293 4.0-7 cells were constructed as described by Rogers et al., J. Bone Miner. Res. 10 Suppl. 1:S483, 1995 (hereby incorporated by reference herein). Intracellular Ca^{2+} increases were elicited by increasing extracellular Ca^{2+} from 1 to 1.75 mM. Intracellular Ca^{2+} was measured using fluo-3, a fluorescent calcium indicator.

The procedure was as follows:

1. Cells were maintained in T-150 flasks in selection media (DMEM supplemented with 10% fetal bovine serum and 200 ug/mL hygromycin B), under 5% CO_2:95% air at 37 ^oC and were grown up to 90% confluency.

2. The medium was decanted and the cell monolayer was washed twice with phosphate-buffered saline (PBS) kept at 37 ^oC. After the second wash, 6 mL of 0.02% EDTA in PBS was added and incubated for 4 minutes at 37 ^oC. Following the incubation, cells were dispersed by gentle agitation.

3. Cells from 2 or 3 flasks were pooled and pelleted (100 x g). The cellular pellet was resuspended in 10-15 mL of SPF-PCB+ and pelleted again by centrifugation. This washing was done twice.

Sulfate- and phosphate-free parathyroid cell buffer (SPF-PCB) contains 20 mM Na-Hepes, pH 7.4, 126 mM NaCl, 5 mM KCl, and 1 mM $MgCl_2$. SPF-PCB was made up and stored at 4 ^oC. On the day of use, SPF-PCB was supplemented

with 1 mg/mL of D-glucose and 1 mM $CaCl_2$ and then split into two fractions. To one fraction, bovine serum albumin (BSA; fraction V, ICN) was added at 5 mg/mL (SPF-PCB+). This buffer was used for washing, loading and maintaining the cells. The BSA-free fraction was used for diluting the cells in the cuvette for measurements of fluorescence.

4. The pellet was resuspended in 10 mL of SPF-PCB+ containing 2.2 uM fluo-3 (Molecular Probes) and incubated at room temperature for 35 minutes.

5. Following the incubation period, the cells were pelleted by centrifugation. The resulting pellet was washed with SPF-PCB+. After this washing, cells were resuspended in SPF-PCB+ at a density of 1-2 x 106 cells/mL.

6. For recording fluorescent signals, 300 uL of cell suspension were diluted in 1.2 mL of SPF buffer containing 1 mM $CaCl_2$ and 1 mg/mL of D-glucose. Measurements of fluorescence were performed at 37 ^{o}C with constant stirring using a spectrofluorimeter. Excitation and emission wavelengths were measured at 485 and 535 nm, respectively. To calibrate fluorescence signals, digitonin (5 mg/mL in ethanol) was added to obtain Fmax, and the apparent Fmin was determined by adding Tris-EGTA (2.5 M Tris-Base, 0.3 M EGTA). The concentration of intracellular calcium was calculated using the following equation:
Intracellular calcium = $(F\text{-}F_{min}/F_{max}) \times K_d$; where $K_d = 400$ nM.

7. To determine the potential calcilytic activity of test compounds, cells were incubated with test compound (or vehicle as a control) for 90 seconds before increasing the concentration of extracellular Ca^{2+} from 1 to 2mM. Calcilytic compounds were detected by their ability to block, in a concentration-dependent manner, increases in the concentration of intracellular Ca^{2+} elicited by extracellular Ca^{2+}.

In general, those compounds having lower IC_{50} values in the Calcium Receptor Inhibitor Assay are more preferred compounds. Compounds having an IC_{50} greater than 50 uM were considered to be inactive. Preferred compounds are those having an IC_{50} of 10uM or lower, more preferred compounds have an IC_{50} of 1uM, and most preferred compounds have an IC_{50} of 0.1uM or lower.

(II) Calcium Receptor Binding Assay

HEK 293 4.0-7 cells stably transfected with the Human Parathyroid Calcium Receptor ("HuPCaR") were scaled up in T180 tissue culture flasks. Plasma membrane is obtained by polytron homogenization or glass douncing in buffer (50mM Tris-HCl pH 7.4, 1mM EDTA, 3mM $MgCl_2$) in the presence of a protease inhibitor cocktail containing 1uM Leupeptin, 0.04 uM Pepstatin, and 1 mM PMSF. Aliquoted membrane was snap frozen and stored at –80 ^oC. ^3H labeled compound was radiolabeled to a radiospecific activity of 44Ci/mmole and was aliquoted and stored in liquid nitrogen for radiochemical stability.

A typical reaction mixture contains 2 nM ^3H compound ((R,R)-N-4'-Methoxy-t-3-3'-methyl-1'-ethylphenyl-1-(1-naphthyl)ethylamine), or ^3H compound (R)-N-[2-Hydroxy-3-(3-chloro-2-cyanophenoxy)propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethylamine 4-10 ug membrane in homogenization buffer containing 0.1% gelatin and 10% EtOH in a reaction volume of 0.5 mL. Incubation is performed in 12 x 75 polyethylene tubes in an ice water bath. To each tube 25 uL of test sample in 100% EtOH is added, followed by 400 uL of cold incubation buffer, and 25 uL of 40 nM ^3H-compound in 100% EtOH for a final concentration of 2nM. The binding reaction is initiated by the addition of 50 uL of 80-200 ug/mL HEK 293 4.0-7 membrane diluted in incubation buffer, and allowed to incubate at 4^oC for 30 min. Wash buffer is 50 mM Tris-HCl containing 0.1% PEI. Nonspecific binding is determined by the addition of 100-fold excess of unlabeled homologous ligand, and is generally 20% of total binding. The binding reaction is terminated by rapid filtration onto 1% PEI pretreated GF/C filters using a Brandel Harvestor. Filters are placed in scintillation fluid and radioactivity assessed by liquid scintillation counting.

Example 1

(E)-3-{3,4-Difluoro-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-acrylic acid ethyl ester (5)

(a) 6-Bromo-2,3-diflurophenol (2) Bromine (4.33 mL, 84.56 mmol) was added dropwise to a vigorously stirred cold (10 ^0C) solution of commercially available 2,3-

difluorophenol (10.00 g, 76.90 mmol) in glacial acetic acid (16 mL) and chloroform (4.0 mL) solvent mixture. After 1 hr the reaction mixture was poured into water (60 mL) and dichloromethane (30 mL) mixture. The aqueous layer was extracted with dichloromethane (3x50 mL) and combined organic layers were washed with sat. $NaHCO_3$ and brine sequentially. Upon drying over Na_2SO_4, it was concentrated to a thick syrup. The crude residue was purified by flash column chromatography (10% ethyl acetate/hexanes) to yield the desired product (2.89 g) in 18% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) □□7.38-7.33 (m, 1H), 6.80-6.30 (m, 1H), 5.94 (brs, 1H).

(b) (R)-2-(6-Bromo-2,3-difluoro-phenoxymethyl)-oxirane (**3**) A solution of 6-Bromo-2,3-difluoro phenol from Example 1a (2.0 g, 9.47 moles) and (2R)-glycidyl 3-nitrobenzenesulfonate (2.45 g, 9.47 moles)) in dry acetone (500 mL) was treated with potassium carbonate (3.93 g, 28.41 moles) and refluxed under nitrogen for 24 h. The reaction was cooled, filtered and filtrate was concentrated in *vacuo* and the residue was flash column chromatographed (25% ethyl acetate/hexanes) to yield the desired product (2.19 g) in 87% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) □□7.55 (dd, J=2.6, 4.1 Hz, 1H), 7.30-7.26 (m, 1H), 6.90-6.83 (m, 1H), 4.40-4.36 (m, 1H), 4.15-4.10 (m, 1H), 3.44-3.40 (m, 1H), 2.91-2.88 (m, 1H), 2.75-2.73 (m, 1H).

(c) [(R)-1-(6-Bromo-2,3-difluoro-phenoxy)-3-(2-indan-2-yl-1,1-dimethyl-ethylamine)-propan-2-ol (**4**) To a solution of the epoxide from Example 1b (2.00 g, 7.55 mmol) and indanyl amine (1.42 g, 7.55 mmol) were taken up in absolute ethanol (75 mL) and refluxed overnight. After all the epoxide was consumed the reaction was cooled and concentrated and purified by flash chromatography (10% methanol/dichloromethane) to yield 80% of the desired product (2.75 g). MS(ES) m/e 455 $[M+H]^+$.

(d) (E)-3-{3,4-Difluoro-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-acrylic acid ethyl ester (**5**) A 75mL sealed tube was charged with a stir bar, the bromide from Example 1c (2.75 g, 6.06 mmol) and propionitrile (30 mL). To this was added $Pd(OAc)_2$ (0.14 g, 0.61 mmol), P(*o*-tol)$_3$

(0.74 g, 2.40 mmol), and ethyl acrylate (1.21 g, 1.21 mol) sequentially. The solution was then deoxygenated by bubbling nitrogen through for 15 minutes. The sealed tube was capped tightly and immersed into a preheated (100^0 C) oil bath. The reaction was heated at this temperature for 12 h, cooled to ambient temperature, and then concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting initially with 50% EtOAc in hexanes and 100% EtOAc. At this time the eluting solvent mixtures were switched to 100% DCM, 5% MeOH in DCM followed by 8% MeOH in DCM. The product was collected and concentrated to provide the title compound (2.37 g) in 82% yield as pale yellow foam. MS(ES) m/e 474 $[M+H]^+$.

Example 2

3-{3,4-Difluoro-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid ethyl ester (6)

The 100 mL round bottom flask was equipped with a magnetic stir bar, acrylic acid ethyl ester from Example 1d (2.37 g) and 30 mL of absolute ethanol. To this was added 0.30 g of catalyst (10% Pd/C) and placed under hydrogen atmosphere. After 16 h of stirring all starting material was consumed. The reaction mixture was filtered though a pad of celite and washed with additional amount of ethanol and concentrated to get the desired product (2.18 g) in 92% yield. The crude ester was purified by reverse phase HPLC to afford the pure compound. MS(ES) m/e 476 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) □□8.41-8.34 (m, 2H), 7.20-7.07 (m, 6H), 5.86 (brs, 1H), 4.14-4.10 (m, 3H), 4.02 (q, J=7.09 Hz, 2H), 3.23-2.86 (m, 9H), 2.59 (t, J=7.3 Hz, 2H), 1.95 (d, J=5.8 Hz, 2H), 1.37 (s, 6H), 1.13 (t, J=7.1 Hz, 3H).

Example 3

3-{3,4-Difluoro-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-propionic acid (7)

A solution of the ester from Example 2 (1.5 g, 3.15 moles) in ethanol (15 mL) was treated with 6N NaOH (3.15 mL, 18.9 moles) and stirred at ambient temperature.

Upon completion of the reaction, ethanol was removed in *vacuo* and the aqueous layer was diluted with water (10 mL) and then extracted with ether (3x100 mL). The aqueous layer was collected and the pH was adjusted to pH 4 with conc.HCl while stirring and extracted with dichloromethane (3x50 mL). Organic layer was dried (Na_2SO_4) and concentrated to a pale yellow foam. This crude material was purified by reverse phase HPLC to afford the pure compound. MS(ES) m/e 448 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) □□12.00 (brs, 1H), 8.40-8.38 (m, 2H), 7.21-7.05 (m, 6H), 5.88 (brs, 1H), 4.14-4.04 (m, 3H), 3.31-2.88 (m, 8H), 2.69-2.53 (m, 3H), 1.94 (d, J=6.0 Hz, 2H), 1.36 (s, 6H).

Example 4

(E)-3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-acrylic acid ethyl ester (14)

(a) 2-Benzyloxy-3-bromo-benzamide (**9**) To a anhydrous acetone solution (330 mL) containing 3-bromosalicilamide (25 g, 0.115 moles) was added potassium carbonate (17.57 g, 0.127 moles) and benzyl bromide (13.70 mL, 0.115 moles) sequentially. The reaction was stirred for 12 hr and at which time it was filtered and concentrated. The crude residue was recrystalized from DCM/hexane to yield the desired product (23.20 g) in 66% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.89-7.18 (m, 8H), 5.25 (s, 2H), 3.35 (brs, 2H).

(b) 2-Benzyloxy-3-bromo-benzonitrile (**10**) The benzamide (20.0 g, 0.065 moles) was dissolved in thionyl chloride (200 mL) and heated to reflux for 12 h. Upon completion of the reaction all thionyl chloride was all evaporated and the resulted residue was redissolved in ethyl acetate (500 mL) and washed with cold water (100 mL) and Brine (100 mL). The organic layer was separated, dried (Na_2SO_4) and concentrated. The residue was recrystalized from DCM/hexanes to give desired product (16.37 g) in 89% yield. MS(ES) m/e 288 $[M+H]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.70 (d, J=8.1Hz, 1H), 7.59 (dd, J=2.5,6.48 Hz, 1H), 7.46-7.34 (m, 5H), 6.91 (d, J=9.0 Hz, 1H), 5.22 (s, 2H).

(c) 3-Bromo-2-hydroxy-benzonitrile (**11**) To a anhydrous dichloromethane solution (75 mL) containing benzyloxy protected benzonitrile (16.37 g) was cooled to –78 °C and treated with 1M solution with of borontribromide (182 mL) in DCM. Upon completion the reaction mixture was poured into EtOAc/ice mixture and the organic layer was separated and washed with Brine (100 mL) and concentrated. The resulting residue was purified by FCC to produce the desired product (9.12 g) in 79% yield. MS(ES) m/e 198 $[H]^+$. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, J=2.37 Hz, 1H), 7.59 (dd, J=2.4, 6.44 Hz, 1H), 6.92 (d, J=9.2 Hz, 1H), 6.00 (brs, 1H).

(d) 3-Bromo-2-(R)-1-oxiranylmethoxy-benzonitrile (**12**) A solution of 3-Bromo-2-hydroxy-benzonitrile (9.12 g, 0.046 moles) and (2R)-glycidyl 3-nitrobenzenesulfonate (11.92 g, 0.046 moles)) in dry acetone (500 mL) was treated with potassium carbonate (19.07 g) and heated to reflux under nitrogen for 24 h. The reaction was cooled, filtered and filtrate was concentrated in *vacuo* and the residue was flash column chromatographed (25% ethyl acetate/hexanes) to yield the desired product (5.12 g) in 44% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.69(d, J=2.37 Hz, 1H), 7.64 (dd, J=2.4, 6.44 Hz, 1H), 6.95 (d, J=9.2 Hz, 1H), 4.40-4.38 (m, 1H), 4.15-4.08 (m, 1H), 3.25-3.21 (m, 1H), 3.18-3.16 (m, 1H), 2.85-2.68 (m, 3H).

(e) 3-Bromo-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-benzonitrile (**13**) A mixture of the epoxide (5.12 g, 0.02 moles) and indanyl amine (3.79 g, 0.02 moles) were taken up in absolute ethanol (92 mL) and heated to reflux overnight. After all the epoxide was consumed, the reaction was cooled, concentrated, and purified by flash chromatography (10% methanol/DCM) to yield 86% of the desired product (7.64 g). MS(ES) m/e 443 $[M+H]^+$.

(f) (E)-3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-acrylic acid ethyl ester (**14**) A 75mL sealed tube was charged with a stir bar, the bromide (1.95 g, 4.4 mmol) and propionitrile (22 mL). To this was added $Pd(OAc)_2$ (0.10 g, 0.44 mmol), P(*O*-tol)$_3$ (0.54 g, 1.76 mmol), and ethyl acrylate (0.96 mL, 8.8 mmol) sequentially. The solution was deoxygenated by

bubbling nitrogen through for 15 minutes. The sealed tube was capped tightly and immersed into a preheated (120^0 C) oil bath. The reaction was heated at this temperature for 12 h, cooled to ambient temperature, and then concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting initially with 50% EtOAc in hexanes and 100% EtOAc. At this time the eluting solvent mixtures were switched to 100% DCM, 5% MeOH in DCM followed by 8% MeOH in DCM. The product was collected and concentrated to provide the title compound (1.91 g) in 94% yield as pale yellow foam. MS(ES) m/e 463 $[M+H]^+$.

Example 5

3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-propionic acid ethyl ester (15)

A 100 mL round bottom flask was equipped with a magnetic stir bar and charged with acrylic acid ethyl ester from Example 4f (2.70 g) and 30 mL of absolute ethanol. To this was added 0.30 g of catalyst (5% $Pd/CaCO_3$), and the mixture was placed under hydrogen atmosphere. After 16 h of stirring, all starting material was consumed. The reaction mixture was filtered though a pad of celite and washed with an additional amount of methanol and concentrated to get the desired product (2.66 g) in 98% yield. The crude ester was purified by reverse phase HPLC to afford the pure compound. MS(ES) m/e 465 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:8.21 (brs, 2H), 7.47 (d, J=2.1 Hz, 1H), 7.40 (dd, J=2.0, 6.7 Hz, 1H), 7.06-6.94 (m, 6H), 5.80 (brs, 1H), 4.07-3.96 (m, 2H), 3.88 (q, J=7.1 Hz, 1H), 3.09 (brs, 1H), 2.97-2.88 (m, 4H), 2.67 (t, J=7.4 Hz, 2H), 2.46 (t, J=7.3 Hz, 2H), 2.44-2.39 (m, 3H), 1.80 (d, J=7.8 Hz, 2H), 1.22 (s, 6H), 1.00 (t, J=7.1 Hz, 3H).

Example 6

3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-propionic acid hydrochloride salt (16)

A solution of the ester from Example 5 (2.0 g, 4.31 mmol) in ethanol (15 mL) was treated with 6N NaOH (4.0 mL, 21.0 mmol) and stirred at ambient temperature. Upon completion of the reaction, ethanol was removed in *vacuo* and the aqueous layer was diluted with water (10 mL) and then extracted with ether (3x100 mL). The aqueous layer was collected and the pH was adjusted to pH 4 with concentrated HCl while stirring. The precipitated white solid was collected by filtration and air dried to afford the corresponding acid. The acid was suspended in dry acetonitrile (10 mL) and treated with 1.0M HCl (5.2 mL) in ether. The reaction was stirred for 15 minutes and then was concentrated to give pale yellow foam (1.30 g) in 64% yield. MS(ES) m/e 437 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:12.00 (brs, 1H), 8.70 (t, J=10.2 Hz, 1H), 8.47 (t, J=10.0 Hz, 1H), 7.51 (d, J=2.2 Hz, 1H), 7.45 (dd, J=2.2, 8.73 Hz, 1H), 7.13-6.99 (m, 5H), 5.86 (brs, 1H), 4.15-4.04 (m, 3H), 3.34-2.93 (m, 6H), 2.69 (t, J=7.4 Hz, 2H), 2.52-2.40 (m, 3H), 1.99 (d, J=6.9 Hz, 2H), 1.29 (s, 6H).

Example 7

(E)-4-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-but-3-enoic acid methyl ester

A 350 ml sealed tube was charged with a stirring bar, 3-Bromo-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino-propoxy]-benzonitrile from Example 4e (7.0 g, 15.8 mmol) and propionitrile (160 ml). To this was added $Pd(OAc)_2$ (0.355 g, 0.1 equiv.), P(*o*-tol) $_3$ (1.92 g, 0.4 equiv), methyl 3-butenoate (3.16 g, 2 equiv.), and triethylamine (6.40 g, 4 equiv.) sequentially, and the mixture was deoxygenated by bubbling nitrogen through for 15 minutes. The sealed tube was capped tightly and immersed into a preheated (120 ^{0}C) oil bath. The reaction was heated at this temperature overnight, cooled to ambient temperature, and then concentrated under

reduced pressure. The crude residue was purified by flash column chromatography eluting initially with 50% EtOAc in hexanes and 100% EtOAc. At this time the eluting solvent mixtures were switched to 100% DCM, 5% MeOH in DCM followed by 8% MeOH in DCM. The product was collected and concentrated to provide the title compound (5.6 g, 76%) as pale yellow foam. MS (ES) m/z 463 $[M+H]^+$

Example 8

4-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-butyric acid methyl ester

A 250 ml round bottom flask was equipped with a magnetic stir bar, the butenoic ester from Example 7 (5.6 g, 12 mmol), and 100 ml of absolute ethanol. To this was added 0.56 grams (10% w/w) of catalyst ($Pd/CaCO_3$), and the mixture was placed under hydrogen atmosphere. Hydrogenation proceeded overnight. The reaction mixture was filtered through a pad of celite and washed with an additional amount of ethanol and concentrated to provide the title compound (5.1 g, 90%). MS (ES) m/z 465 $[M+H]^+$

Example 9

4-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-butyric acid hydrochloride

(a) A solution of ester from Example 8 (2.5 g, 5.4 mmol) in ethanol (30 ml) was treated with 2.5 N NaOH (10 mL, 4.5 eq.) and stirred at RT under argon overnight. The ethanol was removed in *vacuo* and the aqueous layer was diluted with water (10 ml) and then extracted with ether (3x20 ml). The aqueous layer was collected and the pH was adjusted to pH 5 with concentrated HCl while stirring. The precipitated yellow solid was collected by filtration and air dried to afford the title compound (1.5 g, 62%). MS (ES) m/z 451$[M+H]^+$

(b) The acid from Example 9a (0.1 g, 0.22 mmol) was suspended in dry acetonitrile (5 mL) and treated with 2.0M HCl (0.5 mL, 5 equiv.) in ether. The reaction mixture

became homogeneous after a few minutes and then a pale yellow solid precipitated. The reaction was stirred for an additional 10 minutes after which time it was filtered and dried to provide the desired salt (0.081 g, 75%). MS (ES) m/z 451 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6): δ:12.2 (brs, 1H), 8.87 (s, 1H), 8.58 (s, 1H), 7.57 (d, 1H), 7.51 (dd, 1H), 7.28-7.16 (m, 3H), 7.12-7.09 (m, 2H), 5.98 (brs, 1H), 4.26-4.16 (m, 3H), 3.24-3.07 (m, 6H), 2.62-2.47 (m, 3H), 2.19 (t, 2H), 1.97 (d, 2H), 1.78 (t, 2H), 1.39 (s, 6H).

Example 10

4-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1,1-dimethyl-ethylamino)-propoxy]-phenyl}-butyric acid ethyl ester hydrochloride

The acid from Example 9 (0.1 g, 0.22 mmol) was dissolved in absolute ethanol (10 ml), and a catalytic amount of concentrated sulfuric acid was added. The reaction was stirred and heated to reflux overnight. The reaction was concentrated, then diluted with ethyl acetate and washed with 2.5N NaOH (2x5 ml), brine (5 ml), and dried over sodium sulfate. The filtrate was concentrated and purified by HPLC. The TFA salt was converted to the HCl salt to provide the title compound as a pale yellow oil (0.088 g, 77%). MS (ES) m/z 477 $[M-H]^+$ ^1H NMR (400 MHz, DMSO-d_6): δ: 8.58 (s, 1H), 8.43 (s, 1H), 7.57 (d, 1H), 7.51 (dd, 1H), 7.28-7.16 (m, 3H), 7.12-7.09 (m, 2H), 5.94 (brs, 1H), 4.26-4.16 (m, 3H), 4.05 (q, 2H), 3.24-3.07 (m, 6H), 2.62-2.47 (m, 2H), 2.19 (t, 2H), 1.97 (d, 2H), 1.78 (t, 2H), 1.38 (s, 6H), 1.22 (t, 3H).

Example 11

(E)-3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-pent-4-enoic acid ethyl ester

A 75mL sealed tube was charged with a stir bar, the bromide from Example 4e (1.00 g, 2.25 mmol) and propionitrile (22 mL). To this was added $Pd(OAc)_2$ (0.05 g, 0.23 mmol), P(*o*-tol)$_3$ (0.12 g, 0.90 mmol), and 4-pentenoic acid ethyl ester (0.58 g, 4.5 mmol) sequentially. The solution was then deoxygenated by bubbling nitrogen

through for 15 minutes. The sealed tube was capped tightly and immersed into a preheated (120^0 C) oil bath. The reaction was heated at this temperature for 12 h, cooled to ambient temperature, and then concentrated under reduced pressure. The crude residue was purified by flash column chromatography eluting initially with 50% EtOAc in hexanes and 100% EtoAc. At this time the eluting solvent mixtures were switched to 100% DCM, 5% MeOH in DCM followed by 8% MeOH in DCM. The product was collected and concentrated to provide the desired product (0.96 g) in 87% yield as a pale yellow foam. MS(ES) m/e 491 $[M+H]^+$.

Example 12

3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-pentanoic acid ethyl ester

A 100 mL round bottom flask was equipped with a magnetic stir bar, ethyl ester from Example 11 (0.96 g), and 30 mL of absolute ethanol. To this was added 0.20 g of catalyst (5% $Pd/CaCO_3$), and the mixture was placed under hydrogen atmosphere. After 16 h of stirring, all starting material was consumed. The reaction mixture was filtered though a pad of celite and washed with an additional amount of methanol and concentrated to provide the desired product (0.94 g) in 98% yield. MS(ES) m/e 493 $[M+H]^+$.

Example 13

3-{3-Cyano-2-[(R)-2-hydroxy-3-(2-indan-2-yl-1, 1-dimethyl-ethyl amino)-propoxy]-phenyl}-pentanoic acid trifluoroacetate salt

A solution of the ester from Example 12 (0.94 g, 1.91 mmoles) in ethanol (15 mL) was treated with 6N NaOH (4.0 mL, 21.0 mmoles) and stirred at ambient temperature. Upon completion of the reaction, ethanol was removed in *vacuo* and the aqueous layer was diluted with water (10 mL) and then extracted with ether (3x100 mL). The aqueous layer was collected and the pH was adjusted to pH 4 with concentrated HCl while stirring. The precipitated white solid was collected by

filtration and air dried to afford the corresponding acid. The acid was suspended in dry acetonitrile (10 mL) and treated with 1.0M HCl (5.2 mL) in ether. The reaction was stirred for 15 minutes and then concentrated to give pale yellow foam (1.30 g) in 64% yield. The crude ester was purified by reverse phase HPLC to afford the pure compound. MS(ES) m/e 465 $[M+H]^+$. ^{1}H-NMR (400 MHz, DMSO-d_6) δ:8.78 (t, J=10.2 Hz, 1H), 8.50 (t, J=10.1 Hz, 1H), 7.41-7.49 (m, 2H), 6.94-7.06 (m, 5H), 5.60 (brs, 1H), 4.10-4.23 (m, 3H), 2.95-3.35 (m, 6H), 2.50-2.59 (m, 4H), 2.23 (t, J=7.3 Hz, 2H), 1.96 (d, J=5.6 Hz, 2H), 1.47-1.57 (m, 4H), 1.29 (s, 6H).

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the area can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.